Genetics and the Path Towards Targeted Therapies in Systemic Lupus

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Disclosures

• I have the following financial relationships to disclose:
  – Grant/Research support from LabCorp
  – Entitled to receive royalties under a licensing agreement between LabCorp and the University of Minnesota. This relationship has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policies.

• I will discuss the following off label use and/or investigational use in my presentation:
  – Drugs in development or clinical trials for SLE
Why this topic?

• Clinical journals are reporting genetic associations with SLE with increasing frequency
• Interpreting and contextualizing these studies is challenging
• What do we make of genes that are convincingly associated with disease, but we can’t even guess at their function?
• What is the relevance of genetic variants that are significantly associated with disease but have a very small effect, e.g. odds ratio = 1.1?
Pre-2008

Causal variant identified

Potential role unknown

2008-present
Lupus risk genes

Pathways contributing to disease

Targeted therapies

Clinical features
Expression studies
Systemic Lupus Erythematosus

• Complex inflammatory autoimmune disease with multi-system organ involvement
• More frequently affects women (9:1 female gender bias) and non-Caucasians (2- to 4-fold greater prevalence)
• Characterized by pathogenic autoantibody production, particularly against intracellular antigens
• Etiology involves genetic and environmental factors
• Significant clinical heterogeneity
Clinical Phenotypes of SLE

• Diagnosis of SLE
  – American College of Rheumatology established 11 classification criteria
  – A person who fulfills 4 out of 11 criteria has SLE

• In a cohort of 300 SLE patients, we examined the patterns of classification criteria. Example:

<table>
<thead>
<tr>
<th></th>
<th>Malar</th>
<th>Discoid</th>
<th>Photo</th>
<th>Oral</th>
<th>Arthritis</th>
<th>ANA</th>
<th>Serositis</th>
<th>Renal</th>
<th>Neurological</th>
<th>Hematological</th>
<th>Immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

• We observed 175 different patterns of classification criteria.

• Of these 175 patterns, 114 were observed in only a single patient.
Patterns of diagnostic criteria among 300 SLE patients

Number of patterns

Number of times the pattern occurs
<table>
<thead>
<tr>
<th>Malar</th>
<th>Discoid</th>
<th>Photo</th>
<th>Oral</th>
<th>Arthritis</th>
<th>ANA</th>
<th>Serositis</th>
<th>Renal</th>
<th>Neurological</th>
<th>Hematological</th>
<th>Immunologic</th>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

300 patients
<table>
<thead>
<tr>
<th>Malar</th>
<th>Discoid</th>
<th>Photo</th>
<th>Oral</th>
<th>Arthritis</th>
<th>ANA</th>
<th>Serositis</th>
<th>Renal</th>
<th>Neurological</th>
<th>Hematological</th>
<th>Immunologic</th>
</tr>
</thead>
</table>

300 patients
Immunopathogenesis of lupus

Dennis 2012
Lupus risk genes

Pathways contributing to disease

Targeted therapies
Support for a Genetic Component of SLE

- 10-20% of SLE patients have an affected first-degree relative.
- Among siblings, the relative risk ($\lambda_s$) is 20-29.
  - Higher than the relative risk for multiple sclerosis, Grave’s disease, type 1 diabetes, rheumatoid arthritis, and psoriasis.
- Higher concordance of disease in monozygotic twins (>35%) vs. dizygotic twins and other full siblings (2-5%).
- The genetic risk for lupus is likely derived from variation in many (up to 100?) genes, each with modest effect.
Family-based linkage studies
Candidate gene studies
Genome-wide association studies
Genome-wide surveys of genetic variation

- Leverage information from HapMap project about how genetic variance at one locus can predict genetic variance at an adjacent locus.
  - ~10 million single nucleotide polymorphisms (SNPs) occur commonly in the human genome.
  - 300,000-600,000 “tag SNPs” contain most of the information about patterns of genetic variation.
  - GWAS (500,000 SNPs) provide a survey of the genome (3 billion base pairs)

- Facilitate identification of common variants (>5%) that confer small risk of disease (odds ratios of 1.1 – 1.5)
Genome-wide association study (GWAS) approach

• Sample size requirement: Thousands of cases and controls are required (-> consortia)
• Identification of common variants with modest effect sizes (odds ratios close to 1.0)
• Findings must be replicated in other sets of cases and controls
• Limitations
  – Does not identify the causal variant(s)
  – Does not assess other types of variants (insertion/deletion polymorphisms, DNA methylation, etc.)
• More genetic risk factors for common diseases were identified in 2007 ("the year of the GWAS") than had been collectively reported before 2007.
Generation of raw genomewide association data (shown in a Manhattan plot)

Genomewide association using clean data

Test of replication: selected SNPs are genotyped in an independent cohort or case–control set

Quality control and data cleaning

Selection of variants for replication

Hardy 2009
Test of replication: selected SNPs are genotyped in an independent cohort or case–control set.

Selection of variants and data mining at an unequivocally associated locus.

SNPs marking suggestive loci are selected for further tests of replication by genotyping the relevant SNPs in additional cohorts or case–control sets.

Fine mapping of the locus.

Biologic interpretation of linked variants.

Hardy 2009
**GWAS in SLE**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>SLE cases (n)</th>
<th>Controls (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hom</td>
<td>2008</td>
<td>Caucasian</td>
<td>1311</td>
<td>3340</td>
</tr>
<tr>
<td>Harley</td>
<td>2008</td>
<td>Caucasian</td>
<td>729</td>
<td>2337</td>
</tr>
<tr>
<td>Kozyrev</td>
<td>2008</td>
<td>Caucasian</td>
<td>279</td>
<td>515</td>
</tr>
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<td>Graham</td>
<td>2008</td>
<td>Caucasian</td>
<td>431</td>
<td>2155</td>
</tr>
<tr>
<td>Han</td>
<td>2009</td>
<td>Asian</td>
<td>1047</td>
<td>1205</td>
</tr>
<tr>
<td>Yang</td>
<td>2010</td>
<td>Asian</td>
<td>320</td>
<td>1500</td>
</tr>
</tbody>
</table>

- Chip content influences inter-study results (e.g. TNFAIP3, PDCD1)
- Asian studies validated seven previously reported loci and identified nine new SLE susceptibility loci
- An ongoing challenge: Finding false negative signals among the SNPs falling just below the borderline of genome-wide significance
<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Published p value</th>
<th>Published OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BANK1</td>
<td>4q24</td>
<td>$3.7 \times 10^{-10}$ (EU)</td>
<td>1.4</td>
</tr>
<tr>
<td>BLK</td>
<td>8p23.1</td>
<td>$7.0 \times 10^{-12}$ (EU)</td>
<td>1.22</td>
</tr>
<tr>
<td>C1q</td>
<td>6p21.32</td>
<td>$5 \times 10^{-10}$ (EU)</td>
<td>$-5$ to $10$</td>
</tr>
<tr>
<td>C2</td>
<td>6p21.32</td>
<td>$5 \times 10^{-10}$ (EU)</td>
<td>$-5$ to $10$</td>
</tr>
<tr>
<td>C4A/B</td>
<td>6p21.32</td>
<td>$5 \times 10^{-10}$ (EU)</td>
<td>$-5$ to $10$</td>
</tr>
<tr>
<td>CRP</td>
<td>1q23.2</td>
<td>$6.41 \times 10^{-7}$ (AA)</td>
<td>0.49</td>
</tr>
<tr>
<td>ETS1</td>
<td>11q24.3</td>
<td>$1.77 \times 10^{-25}$ (AS)</td>
<td>1.37</td>
</tr>
<tr>
<td>FcGR2A–FcGR3A</td>
<td>1q23.2</td>
<td>$6.78 \times 10^{-7}$ (EU)</td>
<td>0.74</td>
</tr>
<tr>
<td>FcGR3B</td>
<td>1q23.2</td>
<td>$2.7 \times 10^{-8}$ (EU)</td>
<td>$-$</td>
</tr>
<tr>
<td>HIC2–UBE2L3</td>
<td>22q11.21</td>
<td>$7.53 \times 10^{-8}$ (EU)</td>
<td>1.22</td>
</tr>
<tr>
<td>HLA–DR2 and DR3</td>
<td>6p21.32</td>
<td>$1.71 \times 10^{-52}$ (EU)</td>
<td>2.36</td>
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<tr>
<td>IKZF1</td>
<td>7p12.2</td>
<td>$2.75 \times 10^{-23}$ (AS)</td>
<td>0.72</td>
</tr>
<tr>
<td>IL–10</td>
<td>1q32.1</td>
<td>$4.0 \times 10^{-8}$ (EU)</td>
<td>1.19</td>
</tr>
<tr>
<td>IRAK1, MECP2</td>
<td>Xq28</td>
<td>$1.2 \times 10^{-8}$ (EU, AS)</td>
<td>1.39</td>
</tr>
<tr>
<td>IRF5</td>
<td>7q32</td>
<td>$4.4 \times 10^{-16}$ (EU)</td>
<td>1.45</td>
</tr>
<tr>
<td>ITGAM–ITGAX</td>
<td>16p11.2</td>
<td>$1.61 \times 10^{-23}$ (EU)</td>
<td>1.62</td>
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<tr>
<td>JAZF1</td>
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<tr>
<td>KIAA1542/PHRF1</td>
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<td>0.78</td>
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<tr>
<td>LRRC18–WDFY4</td>
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<td>$7.22 \times 10^{-12}$ (AS)</td>
<td>1.24</td>
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<tr>
<td>LYN</td>
<td>8q12.1</td>
<td>$5.4 \times 10^{-8}$ (EU)</td>
<td>0.77</td>
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<tr>
<td>NMMAT2</td>
<td>1q25</td>
<td>$1.08 \times 10^{-7}$ (EU)</td>
<td>0.85</td>
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<tr>
<td>PRDM1, ATG5</td>
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<td>$1.74 \times 10^{-8}$ (EU)</td>
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<td>PTPN22</td>
<td>1p13</td>
<td>$9 \times 10^{-5}$ (EU)</td>
<td>1.4</td>
</tr>
<tr>
<td>PTTG1</td>
<td>5q33.3</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>PXK</td>
<td>3p14.3</td>
<td>$7.10 \times 10^{-9}$ (EU)</td>
<td>1.25</td>
</tr>
<tr>
<td>RASGRP3</td>
<td>2p22.3</td>
<td>$1.3 \times 10^{-15}$ (AS)</td>
<td>0.7</td>
</tr>
<tr>
<td>SLC15A4</td>
<td>12q24.32</td>
<td>$1.77 \times 10^{-11}$ (AS)</td>
<td>1.26</td>
</tr>
<tr>
<td>STAT1, STAT4</td>
<td>2q32.3</td>
<td>$1.9 \times 10^{-9}$ (EU)</td>
<td>1.55</td>
</tr>
<tr>
<td>TNFAIP3</td>
<td>6q23.3</td>
<td>$2.9 \times 10^{-12}$ (EU)</td>
<td>2.3</td>
</tr>
<tr>
<td>TNFSF4</td>
<td>1q25.1</td>
<td>$6.08 \times 10^{-7}$ (EU)</td>
<td>$-$</td>
</tr>
<tr>
<td>TNIP1</td>
<td>5q33.1</td>
<td>$3.8 \times 10^{-13}$ (EU)</td>
<td>1.27</td>
</tr>
<tr>
<td>TREX1</td>
<td>3p21.31</td>
<td>$4.1 \times 10^{-7}$ (EU)</td>
<td>$-25$</td>
</tr>
<tr>
<td>UHRF1BP1</td>
<td>6p21.31</td>
<td>$2.22 \times 10^{-8}$ (EU)</td>
<td>1.17</td>
</tr>
<tr>
<td>XRK6</td>
<td>8p23.1</td>
<td>$2.51 \times 10^{-11}$ (EU)</td>
<td>1.23</td>
</tr>
</tbody>
</table>

AA, African-American; AS, Asian; EU, European; SLE, systemic lupus erythematosus.
So we have this list of genes.  
What do we know?
Lupus risk genes → Pathways contributing to disease → Targeted therapies
Major pathways represented among known SLE genes

Nature Reviews | Genetics

Harley 2009
Toll-like receptor (TLR) and type I interferon (IFN) signaling

- SLE patients have increased serum levels of IFN-alpha (Hooks 1979)
- A subset of patients treated with IFN-alpha for non-autoimmune disorders develop a lupus-like syndrome
- Blood cells from SLE patients have an IFN-inducible gene signature (Baechler 2003, Bennett 2003); a similar signature is observed in affected tissues (kidney, skin)
- The SLE IFN signature is a biomarker for active disease and defines a subgroup of patients with severe SLE (Kirou 2005, Bauer 2009, Petri 2009)
- Nucleic-acid containing immune complexes from SLE patients can trigger activation of TLRs that normally respond to viral or bacterial nucleic acid, leading to type I IFN production
An IFN gene signature in blood cells of patients with severe SLE

Baechler 2006
Infection

Lymph node

Activated

DC

Type I IFN

Plasmacytoid DC

Monocyte

Activated DC

Persistent apoptotic material

Auto-antibodies

B cell

T cell

Lymph node

Baechler 2003
TLR and IFN signaling

- **IRF5** (IFN regulatory factor 5)
  - Regulates type I IFN-responsive genes; positive feedback loop w/ IFNα
- **IRAK1** (interleukin-1 receptor associated kinase)
  - Toll/IL-1 receptor family signaling
  - Murine studies suggest a role for IRAK1 in induction of IFN and TLR activation
- **STAT4** (signal transducer and activator of transcription 4)
  - Transmits signals following cytokine and growth factor signaling
  - Risk variant confers an increased sensitivity to IFNα
- **TNFAIP3** (TNFα-induced protein 3)
  - Terminates proinflammatory responses downstream of TLRs
- **Osteopontin** (SPP1)
  - A bone matrix mediator with roles in inflammation and immunity; overexpressed in SLE patients
  - Critical for IFNα production in murine pDCs
- **TREX1** (3’ DNA repair exonuclease 1)
  - TREX1-deficiency impairs DNA damage repair, leading to the accumulation of endogenous retroelement-derived DNA. Defective clearance of this DNA induces IFN production and an immune-mediated inflammatory response.
Major pathways represented among known SLE genes

Harley 2009
Lymph node
Activated DC

T cell
B cell

Type I IFN

Monocyte

Activated DC

Plasmacytoid DC

Persistent apoptotic material

Auto-antibodies

Lymph node
Immune complexes in lupus

- Clearance of immune complexes by mononuclear phagocytes depends on the function of Fcγ receptors and complement receptors
- In SLE, impaired clearance results in immune complex deposition, release of inflammatory mediators, and influx of inflammatory cells
Immune complex processing

• In lupus, C2, C4A, C4B, and C1q exhibit associations with very strong effect sizes through recessive inheritance of uncommon alleles.

• Multiple members of the Fcγ receptor family have been associated with SLE.
  – Missense mutations of activating receptors FCGR2A and FCGR3A alter their affinity for particular subclasses of IgG.

• C-reactive protein (CRP) binds FcγRI, FcγRIIB, and FcγRIIA on the surface of leukocytes.
  – CRP binding to FcγRI or FcγRIIA leads to phagocytosis and the release of inflammatory cytokines; binding to FcγRIIB blocks its activating signals.

• ITGAM (Mac-1, CR3, and CD11b/CD18) functions in immune complex clearance and leukocyte activation, adhesion and migration from the bloodstream.
Major pathways represented among known SLE genes

Harley 2009
Lymphocyte signaling

- **PTPN22**
  - Encodes the lymphoid-specific tyrosine phosphatase (LYP)
  - Risk variant disrupts the interaction of signaling molecules downstream of the T cell receptor
- **TNFSF4 (OX40L)**
  - Provides costimulation to T cells
- **PD-1 (PDCD1)**
  - Inhibitory receptor that down-regulates T and B cell activity.
  - The risk SNP lowers the threshold for resisting immune responses against self.
- **BANK1 (B cell scaffold protein with ankyrin repeats)**
  - B cell adaptor protein.
  - Risk SNPs thought to lead to an altered B cell activation threshold.
- **LYN**
  - Protein tyrosine kinase that physically associates with the B cell receptor and binds to BANK1
- **BLK (B lymphoid tyrosine kinase)**
  - Involved in development of B cells before the appearance of the B cell receptor.
  - Risk variant is associated with reduced expression of BLK mRNA
Harley 2009
What are the contributions of these risk genes in different racial groups?

• Non-Caucasians are disproportionately affected by SLE

• The first GWAS studies focused on Caucasians

Table 3  Groups of genes according to similarity and difference between ethnic groups

<table>
<thead>
<tr>
<th>Characters of genes</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent association</td>
<td>STAT4, TNFAIP3,</td>
</tr>
<tr>
<td>with similar frequency</td>
<td>BANK1, IRAKI1/MECP2</td>
</tr>
<tr>
<td>Consistent association</td>
<td>BLK, IRF5</td>
</tr>
<tr>
<td>with different frequency</td>
<td></td>
</tr>
<tr>
<td>Allelic heterogeneity</td>
<td>HLA-DRB1, FcGRs, IRF5</td>
</tr>
<tr>
<td>Genetic heterogeneity*</td>
<td>PTPN22, ITGAM, PXK, LYN</td>
</tr>
</tbody>
</table>

Bae 2010
Sharing of autoimmune risk genes across different diseases

Delgado-Vega 2010
Zhernakova 2009
Shared loci across different diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>T-cell differentiation</th>
<th>Immune-cell activation, signalling</th>
<th>Innate immunity and TNF signalling</th>
<th>Other categories</th>
<th>Inflammatory bowel disease shared</th>
<th>Disease-specific or shared but with unknown function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>STAT4*</td>
<td>PTPN22*</td>
<td>IRF5*</td>
<td>None</td>
<td>None</td>
<td>ICA1, PHRF1, NMNAT2, PXK, SCUBE1, 1q23.1, 5q33.3</td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>IL23R*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>ERAP1</td>
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<tr>
<td>Asthma</td>
<td>None</td>
<td>None</td>
<td>TRAF1–C5*</td>
<td>None</td>
<td>None</td>
<td>ORMDL3*</td>
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<tr>
<td>Autoimmune thyroid disease</td>
<td>None</td>
<td>None</td>
<td>CTLA4*</td>
<td>None</td>
<td>None</td>
<td>TSHR</td>
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<td>Coeliac disease</td>
<td>IL2–IL21*, IL18RAP*, IL12A</td>
<td>SH2B3*, TAGAP</td>
<td>TNFAIP3*</td>
<td>CCR1–3</td>
<td>None</td>
<td>LPP, RGS1</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>IL12B*, IL18RAP*, IL23R*, STAT3</td>
<td>PTPN22*</td>
<td>IRF5*, TNRSF56B*, IRF5, TNRSF18, IRGM, LRRK2–MUC19, NOD2, ATG16L1</td>
<td>CCR6</td>
<td>None</td>
<td>MST1–BSN*, NKX2–3*, PSMG1*</td>
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<td>Multiple sclerosis</td>
<td>IL2RA*</td>
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<td>IL7R*</td>
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<td>None</td>
<td>CLEC16A*</td>
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<td>Psoriasis</td>
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<td>None</td>
<td>None</td>
<td>ZNF313</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>STAT4*</td>
<td>PTPN22*</td>
<td>IRF5*, CD40, PRKCC, PIF4K2C</td>
<td>CCL21</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>IL2–IL21*, IL2RA*</td>
<td>CTLA4*, PTPN22*, PTPN22*</td>
<td>IRF5*, TNFRSF14, IFIH1</td>
<td>IL7R*</td>
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<td>None</td>
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<td>Ulcerative colitis</td>
<td>IL10</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>MST1–BSN*, NKX2–3*, PSMG1*</td>
</tr>
</tbody>
</table>

Zhernakova 2009
Is there evidence for genes that are associated with specific sub-phenotypes of SLE?
Identification of genes associated with sub-phenotypes of SLE

• 22 known risk SNPs were tested in 1919 SLE patients for association with SLE sub-phenotypes (Taylor 2011)
  – 11 ACR classification criteria
  – Anti-dsDNA production
  – Age at diagnosis

• Individual SNPs were considered as well as a composite genetic risk score (summation of SLE risk alleles with each weighted by its SLE odds ratio)
Association of sub-phenotypes with SLE risk genes

Subphenotypes most associated with cumulative Genetic Risk Score:
- age at diagnosis
- immunologic disorder
- anti-dsDNA antibodies
- hematologic disorder
- oral ulcers (protective)

Subphenotypes most associated with single known genes:
- renal disorder
- arthritis (protective)

Subphenotypes not associated with known SLE susceptibility genes, potentially non-genetic:
- malar rash
- discoid rash
- photosensitivity
- serositis
- neurologic disorder

Taylor 2011
Lupus risk genes

Pathways contributing to disease

Targeted therapies
Treatments for SLE

• FDA approved therapies for SLE:
  – Aspirin (1948)
  – Hydroxychloroquine (1955)
  – Corticosteroids (1955)
  – Belimumab (2011)
Belimumumab

- First new drug approved for SLE in >50 years
- Monoclonal antibody that inhibits B-cell activating factor (BAFF/BLYS).
- BAFF is a cytokine that supports survival and differentiation of B cells.
- BAFF levels are increased in serum and tissues of SLE patients.
- Inhibitors of BAFF and its homolog APRIL have been successful in murine models of lupus.
Effects of BAFF in SLE
# Targeted biologics for SLE

## Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target</th>
<th>Trial phase</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>Phase II</td>
<td>Endpoints not met, under evaluation</td>
<td>78</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>CD20</td>
<td>Phase II</td>
<td>Early terminated trial: under evaluation</td>
<td>79</td>
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<tr>
<td>Epratuzumab</td>
<td>CD22</td>
<td>Phase II</td>
<td>Dose-finding study</td>
<td>80</td>
</tr>
<tr>
<td>Belimumab</td>
<td>BLyS</td>
<td>Phase III</td>
<td>Two phase III trials met primary endpoint</td>
<td>70 81</td>
</tr>
<tr>
<td>Atacicept</td>
<td>BLyS and APRIL</td>
<td>Phase II/III</td>
<td>Under evaluation</td>
<td>82</td>
</tr>
<tr>
<td>BG9588</td>
<td>CD40 ligand</td>
<td>Phase I/II</td>
<td>Thrombotic complications</td>
<td>83 84</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA4</td>
<td>Phase II</td>
<td>Endpoints not met</td>
<td>85</td>
</tr>
<tr>
<td>Infliximab, etc</td>
<td>TNF</td>
<td>NA</td>
<td>Increased anti-dsDNA, anecdotal reports of efficacy in severe lupus</td>
<td>85</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6R</td>
<td>Phase I</td>
<td>In progress</td>
<td>85 86</td>
</tr>
<tr>
<td>MEDI-545</td>
<td>IFNα</td>
<td>Phase II</td>
<td>In progress</td>
<td>87</td>
</tr>
<tr>
<td>Rontalizumab</td>
<td>IFNα</td>
<td>Phase II</td>
<td>In progress</td>
<td>88</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>C5</td>
<td>Early reports</td>
<td>Some early evidence of possible use in TMHA syndromes (acquired TTP-like syndromes)</td>
<td>89</td>
</tr>
<tr>
<td>Lupuzor</td>
<td>CD4 T cells relevant to anti-RNP production</td>
<td>Phase II</td>
<td>Subgroup analysis indicated a possible efficacy signal</td>
<td>90</td>
</tr>
</tbody>
</table>

RNP, ribonuclear protein; SLE, systemic lupus erythematosus; TMHA, thrombotic microangiopathic haemolytic anaemia; TTP, thrombotic thrombocytopenic purpura.
How can knowledge of the genetics of SLE drive new treatments?

• New understanding of underlying mechanisms may lead to new targets, or finer resolution of current targets
  – Characterizing the function of SLE risk genes whose role in promoting autoimmunity is still unknown may reveal new targets for therapy
  – Further study of IFN-related risk genes may suggest ways to target the IFN pathway with more precision

• Incorporation of risk genotypes into analysis of clinical trials may reveal sub-populations most likely to benefit (or most likely to experience adverse effects)
  – Patients who are genetically predisposed to have increased IFN pathway activation may be more likely to respond to anti-IFN therapies
Type I IFN Blockade

• Type I IFNs are implicated in the pathogenesis of SLE
• Expression levels of IFN-inducible mRNA transcripts and serum proteins are biomarkers for lupus disease activity
• Several SLE risk genes are IFN-related
• Two anti-IFNα antibodies are in clinical trials for SLE
• IFN-inducible transcripts and proteins may be useful pharmacodynamic markers for dose selection
• IFN-related biomarkers may be useful in identifying patients most likely to respond to anti-IFN therapy
Neutralization of IFN-inducible genes after anti-IFNα treatment

- Fully human monoclonal antibody that binds to a majority of the subtypes of human IFNα and inhibits IFN-mediated signaling.
- Phase Ia trial in mild to moderate SLE with cutaneous involvement
- Gene expression microarray profiling of blood and lesional skin of treated patients.
- 37 patients with moderate to high IFN signatures were selected for monitoring response of the IFN signature to anti-IFNα treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of SLE patients</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
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<tr>
<td>0.3 mg/kg</td>
<td>5</td>
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<tr>
<td>1.0 mg/kg</td>
<td>6</td>
</tr>
<tr>
<td>3.0 mg/kg</td>
<td>6</td>
</tr>
<tr>
<td>30.0 mg/kg</td>
<td>4</td>
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</table>

Yao 2009
Is the IFNα-inducible gene expression signature in SLE blood cells neutralized after treatment of patients with an anti-IFNα mAb?
Reduced expression of IFN-inducible genes in blood cells after anti-IFNα treatment

* p<0.05 vs. placebo (day 14)
Anti-IFNα: Remaining questions

• Does neutralization of the IFN signature correlate with clinical improvement after anti-IFNα treatment?
• Does the presence of an elevated IFN signature pre-treatment predict response to anti-IFNα therapy?
• Do IFN-related SNPs predict response to treatment and/or neutralization of IFN signatures?
• Are adverse events (infection?) associated with pre-treatment IFN signatures?
- Identification of causal variants
- Characterization of genes whose role is poorly understood
- Other types of variation (epigenetics, CNVs, etc.)
- Gene-gene and gene-environment interactions
Lupus risk genes

Pathways contributing to disease

Targeted therapies

- Understanding the biological mechanisms underlying SLE
- Hypothesis generation driving development of new drugs
- Better characterization of individual patients to promote better use of existing/future treatments